Three-dimensional regional bi-ventricular shape remodeling is associated with exercise capacity in endurance athletes.

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Abstract

Aims: Endurance athletes develop cardiac remodeling to cope with increased cardiac output during exercise. This remodeling is both anatomical and functional and shows large interindividual variability. In this study, we quantify local geometric ventricular remodeling related to long-standing endurance training and assess its relationship with cardiovascular performance during exercise.

Methods: We extracted 3D models of the biventricular shape from end-diastolic cine Magnetic Resonance images acquired from a cohort of 89 triathlon athletes and 77 healthy sedentary subjects. Additionally, the athletes underwent Cardio-Pulmonary Exercise Testing, together with an echocardiographic study at baseline and few minutes after maximal exercise. We used Statistical Shape Analysis to identify regional bi-ventricular shape differences between athletes and non-athletes.

Results: The ventricular shape was significantly different between athletes and controls ($p<1e-6$). The observed regional remodeling in the right heart was mainly a shift of the right ventricle (RV) volume distribution towards the right ventricular infundibulum, increasing the overall right ventricular volume. In the left heart, there was an increment of left ventricular mass and a dilation of the left ventricle. Within athletes, the amount of such remodeling was independently associated to higher peak oxygen pulse ($p<0.001$) and weakly with greater RV Global Longitudinal Strain reserve ($p=0.03$).

Conclusions: We were able to identify specific bi-ventricular regional remodeling induced by long-lasting endurance training. The amount of remodeling was associated with better cardiopulmonary performance during an exercise test.

Keywords: exercise physiology, athlete's heart, cardiac remodeling, statistical shape analysis

Abbreviation List

- AUROC: Area under receiver operator characteristic
- BSA: body surface area
- CO: cardiac output
- CPET: cardiopulmonary exercise testing
- HR: heart rate
- LH: left heart
- LOO-CV: leave one out cross validation
- LV: left ventricle
- LVGLS: left ventricular global longitudinal strain

- LVOT: left ventricular outflow tract
- MRI: magnetic resonance imaging
- PCA: principal component analysis
- PER: pulmonary extraction ratio
- PLS: partial least squares
- RA: right atria
- RH: right heart
- RV: right ventricle
- RV-FW: right ventricular free wall
- RVGLS: right ventricle global longitudinal strain
- RVOT: right ventricle outflow tract
- SA: short axis
- SSA: statistical shape analysis
- STD: standard deviation
- VO_2: oxygen uptake

Background

As reported in the literature, extensive periods of physical exercise result in chronic exposure to volume and pressure overload, inducing cardiac remodeling (La Gerche et al. 2013; Schmied and Borjesson 2014). This cardiac remodeling includes a set of morphological and functional changes to obtain a better cardiovascular response to exercise. Known examples of such remodeling are left ventricle (LV) hypertrophy and dilatation, dilated right ventricle (RV) and atria (RA), decreased resting heart rate (HR) and a slight decrease in myocardial deformation at rest. These changes vary importantly among individuals, but remodeling is consistently more present in the Right Heart (RH) (Rhodes et al. 1990; La Gerche et al. 2012; D'Andrea et al. 2015), which is exposed to a bigger relative pressure increase during exercise in comparison to baseline than the left heart (LH). Exercise-induced remodeling is known to be influenced by lifestyle parameters such as sport discipline, training load and individual-specific parameters such as age, gender, ethnicity (Sanz-de la Garza et al. 2017; Sitges et al. 2017). However, the details and spectrum of physiological adaptation to sport is not yet completely understood.

Geometric assessment of cardiac structures in the clinical community is still predominantly focusing on sparse length/volumes measurements rather than 3D shape patterns. These measurements are insufficient to analyze regional differences, and especially cannot account for the RV shape complexity and variability. Statistical Shape Analysis (SSA) denotes a set of techniques that compute a reference shape for a population and subsequently describe each individual shape with the transformation from the template to this individual (Dryden and Mardia 1998). These techniques have been applied to find regional morphology and deformation differences between two different populations (De Craene et al. 2012; Zhang et al. 2014; Varela et al. 2017; Varano et al. 2018).

This paper uses SSA methods to find regional differences between bi-ventricular shapes, as retrieved from magnetic resonance imaging (MRI), of endurance athletes and non-athletes and relate these to exercise response and classical imaging parameters. Given that the RH plays a crucial role during exercise, and that its complex shape is difficult to assess using traditional clinical image-based measurements, the proposed approach is particularly suited to study exercise-induced shape alteration in the RH.

Methods

Population

A cohort of healthy 89 triathlon athletes and 77 controls was recruited at Hospital Clínic, Barcelona, according to an internal research protocol validated by the internal ethical committee, and written informed consent was obtained for each of the participants. The triathlete inclusion criteria implied that they exercised at least 10 hours weekly for at least 5 years. They were evaluated via a physical activity questionnaire (Ainsworth et al. 2011). Controls were randomly selected from the birth registry between years 1975 and 1995 in a tertiary university hospital in Barcelona. All individuals included in this study were asymptomatic with no previous known cardiovascular illnesses and no cardiac disease detected on echocardiography.

Echocardiographic measurements

Echocardiographic images for athletes were acquired with a commercially available ultrasound system (Vivid Q; GE Medical; Milwaukee, USA) with a 2.5 MHz (M5S) and an active matrix 4-dimensional volume phased array transducer in the case of the controls. Images were acquired from the parasternal (long- and short-axis) and apical (RV-focused 4-, 4-, 3- and 2-chamber) views. Three consecutive cardiac cycles for each acquisition were digitally stored in a cine loop format for off-line analysis with commercially available software (EchoPac GE, Vingmed). Cardiac chamber dimensions were measured according to the standards of the European Society of Echocardiography and indexed for body surface area according to the DuBois formula (Du Bois and Du Bois 1916). RV end-diastolic area and end-systolic area were estimated by tracing the endocardium from a RV-focused apical 4-chamber view. LV volumes and LV ejection fraction were derived using the biplane Simpson method. Myocardial deformation of both ventricles was evaluated by 2D-STE (2Dstrain, Echo Pac, version 202.41.0, General Electric Healthcare, Milwaukee, WI, USA). Global RV peak systolic strain (RVGLS) was measured as an average of all six RV segments (3 RV-FW and 3 inter-ventricular septum). Left ventricle global longitudinal strain (LVGLS) was calculated as an average of LV systolic strain in 2-, 3- and 4-chamber apical views (Lang et al. 2015).

Exercise Test

All individuals performed an standard incremental cardiopulmonary exercise testing in an up-right position on an electrically braked cycle ergometer (range 6-999 watts) using an Ergoselected 100 (Ergoline, Bitz, Germany). Over the course, of this test, they performed an increasingly demanding exercise until exhaustion, while their gas exchange parameters and HR were being monitored using a breath-by-breath and a 12 lead ECG. From this, the peak and basal oxygen uptake, as well as the HR were measured using the ExpAir software (Medisoft, Sorinnes, Belgium). All measurements were performed according to international guidelines (Ross et al. 2003; Albert et al. 2008).

Athletes were subjected to a post-exercise echocardiographic exam. Immediately after the end of the exercise test, they were moved to a bed next to the ergometer and were scanned to assess function and geometry changes occurring during exercise.

MRI study

Cardiac MRI studies were performed using a 3T (72 athletes and 77 controls) or 1,5T (17 athletes) scanner (Magnetom Trio Tim and Magneton Aera respectively, *Siemens* Medical Solutions, Erlangen, *Germany)* in all subjects involved in this protocol. Images were acquired during apnea. A cine sequence in short axis (SA) view was acquired with 8mm slice thickness, an interslice gap ranging from 0 to 2.4mm, and a pixel size ranging between 0.8 to 1.5 mm.

For each individual in our population, we generated a 3D surface by fitting a whole-heart deformable template, for all time instances, to the SA MRI, using the algorithm described and validated in (Ecabert et al. 2006; Peters et al. 2010). From this, we extracted the LV end-diastolic (ED) frame and selected the LV epicardial and endocardial surfaces as well as the RV endocardium. All contour points were in one-to-one correspondence due to the model-based segmentation.

An expert visually checked all automatic segmentations in the SA, and 2 individuals were discarded for inadequate tracing of the ventricular contour. In the supplementary material S1 we show randomly selected examples of the segmentation contours.

Statistical Shape Analysis

We represented the surfaces/shapes by a Point Distribution Model (PDM) (Cootes et al. 1995), and we used Partial Procrustes Analysis to rigidly align each individual to a common position, thus removing positioning-related variability.

We used Principal Component Analysis (PCA), and Partial Least Squares (PLS) to build a dimensionality reduction that encoded most of the shape variability that correlated with the athlete label. First, we used PCA to obtain a dimensionality reduction that kept 95% of the shape variability, serving as a denoising step. Then, we used PLS to further reduce the shape space to 4 modes that maximized covariance with the athlete label. Finally, we used Logistic Regression (LR) to find an optimal separation between athletes and controls in that reduced space, adjusting by BSA, age and gender as covariates. This LR corresponded to a certain shape pattern, the *athletic remodeling,* that subsequently could be quantified for each individual and expressed as a *remodeling score*.

To verify the model's invariance to age and gender, we used the same SSA method as described above to obtain the athletic remodeling shape pattern, after gender-stratifying the population, as well as with an age-equalized subpopulation. We computed the Pearson's correlation coefficient between remodeling scores obtained with the restricted datasets and the remodeling scores derived from the full dataset.

Statistical methods

We tested the difference of scalar variables using the Mann-Whitney U-test, and the Chi-Square test for categorical variables. We used Multivariate Regression (MVR) to assess the relationship between the athletic remodeling score and the scalar measurements, independently of the confounding variables (BSA, gender and age) that are introduced as covariates in the model. To assess the results of the MVR, we report the p-value using the Fisher F-test, comparing with a model with only the confounding variables as predictors, and the standardized regression coefficient associated with the remodeling score and the R^2 determination coefficient of the model as effect size.

The performance of a logistic model was evaluated using the Area Under Curve (AUC) of the Receiver Operator Characteristic (ROC). We evaluated the models using leave one out cross validation (LOOCV) to split the data in a derivation and validation cohorts without loss of sample size. We compared the SSA model with a simple LR using the confounding variables via a DeLong test (DeLong et al. 1988).

We implemented the analysis in Python 2.7.14 (Enthought Inc, Austin USA), with the following packages: numpy (v1.13.0), scikit-learn(v0.18.1) and scipy(v0.19.0) and RStudio 1.1.423 (RStudio Inc, Boston MA) with package pROC(Robin et al. 2011). We set a threshold of 0.05 to determine statistical significance.

Results

Population characteristics

The population demographics and functional echocardiographic-based parameters are reported in Table 1. Athletes had a lower deformation, BSA and resting HR, which is consistent with chronic exercise, and were 2 years older than controls. Their CO indexed by BSA is maintained. Table 2 shows the comparison geometric MRI-based measurements between athletes and controls. We found an overall increase of the ventricular size. Table S2.1 of the supplementary material shows the difference between resting state and after maximal exercise in athletes.

Athletic shape remodeling

We built a model that captures the differences in 3D shape between athletes and non-athletes using our SSA technique described in the methodology. The model output is a shape pattern that best discriminates between athletes and controls and is therefore the remodeling acquired due to the practice of sport. To visualize that remodeling, in Figure 2 we show the mean shape computed from the controls only, as well as the shape obtained by adding the remodeling with 3 STD of the found athletic shape pattern, thus representing the shape of an extreme athlete. Supplementary material S3 shows a continuous animation of this remodeling. A qualitative assessment of the figure shows that shape remodeling is concentrated in the RV: the outflow and RV apex of the extreme athlete are considerably dilated and more spherical than the mean control. Finally, for each athlete, we quantified how much of this athletic remodeling was present in their individual cardiac shape, to study the relation to acute exercise response. We normalized such score to have 0 mean and 1 STD in the controls.

Exercise response

Using MVR, we investigated in the athletes how different degrees of athletic shape remodeling corresponded to cardiovascular performance in the stress test. *Table 3* shows the standardized regression coefficients of the remodeling score with p-values. All models used age, BSA and gender as covariates.

We found a negative association of athletic shape remodeling to both resting and maximal HR ($p=0.03$, $R^2=0.08$; $p=0.08$, $R^2=0.19$ respectively). Resting VO_2 was not associated to athletic remodeling, but peak VO_2 and peak O_2 pulse were ($p<0.01$, $R^2=0.49$; $p<0.001$, $R^2=0.51$). There was an association between athletic remodeling and greater RVGLS reserve ($p=0.03$, $R^2=0.24$). Neither resting nor post-exercise LVGLS were associated to shape remodeling. While the athletic remodeling score was associated with larger cavities at rest, we found no association with acute RV/LV dilation during the maximal stress test.

Validation

We compared the AUC of the shape's model (AUC = 0.91) and that of a LR that only takes confounding variables into account (AUC = 0.71). The improvement due to the inclusion of shape was statistically significant according to the DeLong test ($p<1e-6$). The ROC of both models can be found in supplementary material S4. In supplementary material S5, we compared our athletic remodeling score with the classical indices used to assess athletic

morphological remodeling (LV mass, LVEDV, RVEDV). Our score was very correlated to these indices and had a slightly better performance at discriminating athletes and controls.

The gender stratified models presented a very strong correlation with the pooled model ($\rho = 0.92$ for the females-only model, and $\rho = 0.93$ for the males-only model). While we observed no gender differences in the most discriminative shape pattern, men presented a higher quantity of remodeling than women. The full experiments for the gender stratified models can be found in the supplementary material S7. The age equalized model presented an almost perfect with the pooled model ($\rho = 0.98$). The full results regarding age can be found in the supplementary materials S7.

Discussion

Complementary to the well-known differences in size and mass, we found strongly significant statistical differences in resting ventricular regional shape between athletes and controls. Within athletes, those differences are positively associated with better performance in an exercise test, as measured by VO_2 uptake. There was a small, yet significant (p=0.03), positive relation with RVGLS reserve. We found a negative, non-significant, association with maximal and resting HR and no association with baseline VO_2 uptake or CO.

The identified athletic LV remodeling corresponds to a dilation and increased myocardial mass compared to the control LV, resulting in a more spherical LV. The ventricular dilation is an adaptation to increase the stroke volume, and the increased sphericity and hypertrophy, help to maintain wall stress limited when the pressure increases during exercise. The RV presents a different type of remodeling: the global effect is an increase in volume, but that increase is not homogeneous and is more prominent in the outflow. RV shape becomes more elongated in the inlet, and there is a shift of volume from inlet to outflow, that is dilated and more spherical. In conclusion, the RV remodeling corresponds more to a change in shape rather than in size while the LV mostly dilates homogenously.

The different behavior of the RV and LV can be explained from its intrinsic different morphological characteristics, as well as the changes in loading conditions induced by exercise. The RV is more compliant and elastic than the LV since LV cavity has not been observed to increase acutely in size during extended submaximal exercise, while RV size can increase up to 10% during moderate exercise (Claessen et al. 2014). Thus, the RV can change shape acutely. The pulmonary artery and aorta also have very different behavior and characteristics with the pulmonary artery being more compliant than the aorta (Slife et al. 1990; Marcus et al. 1994). Additionally, the pressure increases proportionally more in the pulmonary artery during exercise, which translates to RV loading (Kovacs et al. 2009; La Gerche et al. 2017). This is consistent with the observed remodeling in the RV outflow. Another contributing factor, which could not be assessed using the currently available data, might be the induced hypertrophy in the trabeculated RV apex, thus effectively reducing the potential apical stroke volume and forcing the base to remodel accordingly.

Our data show that athletic remodeling at rest has a clear relationship with exercise response: athletes with more remodeling can reach bigger VO_2 max and O_2 pulse. Via Fick's Principle, O_2 uptake can be used to obtain an estimate of the CO during exercise, even when the pulmonary extraction ratio (PER) is not known (Stringer et al. 1997). In (La Gerche et al. 2010), La Gerche et al. reported that the PER interindividual variability was independent of physical training, so we can conclude that the differences in VO_2 max and O_2 pulse were due to differences in CO and SV respectively. Since we found no correlation of athletic remodeling and acute changes of ventricular geometry during exercise, we suggest that the higher SV might be caused by increased deformation during exercise, explained by the weak link between athletic remodeling and RV GLS reserve.

The long-term consequences of this remodeling are unknown, as follow-up is not available, but remodeling seems positive, given that it is correlated with a better cardiovascular response.

Limitations

The SA MRI images had lower quality in the apical part due to the low resolution in the axial direction, and the presence of trabeculations making distinguishing between cavity and myocardium difficult. Therefore, while standard practice, using only MRI SA to construct the 3D model is not ideal to evaluate the apical region and apical differences between the populations might have stayed undetected due to this. Additionally, we did not manually correct the automatic segmentations contours in the images, to better maintain the point-to-point correspondence. We treated these segmentation errors as measurement error in the analysis. Finally, the atria were not included in the image and therefore we could not evaluate them using SSA.

The echocardiographic assessment was done pre- and post-exercise. Given the rapid recovery of athletes, moving them quickly from the exercise bike to the scanning table can affect the post-exercise analysis. Assessing shape during exercise would allow to better understand the acute changes occurring during exercise and characterize the relationship between athletic shape remodelling and cardiovascular response to exercise.

As stated, there is no follow-up data to confirm the positive effect of this remodeling. It must be studied if this remodeling, that dilates the RV outflow, has any relationship with arrhythmogenic right ventricle outflow in the long term.

Conclusion

This paper uses SSA to identify chronic resting shape remodeling induced by endurance sport in both ventricles, using MRI. This remodeling consists of an LV increase in size and myocardial mass, and a shape change in the RV: a shift of the volume distribution from the inlet towards the outflow. Since RV remodeling is concentrated in the outflow, it adds more evidence to the importance of the pulmonary circulation in athletes. After quantifying the remodeling in all athletes, we found that during acute exercise, it is associated to maximal O_2 consumption, O_2 pulse and, weakly, to RV GLS reserve: athletes with more athletic remodeling showed better cardiovascular exercise performance.

As future work, SSA could be used to find regional shape differences induced by pathological remodeling (hypertrophic cardiomyopaties, arrhythmogenic right ventricle) that might have an overlapping remodeling with the athlete's heart, and where current clinical measurements are not well discriminating.

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Conflicts of interest

GB and MDC were working for Philips at the time of the work.

Contributions

ASM, MRL and FC acquired and measured the echocardiography and MRI controls data. MSDG acquired and analyzed the echo data for the athletes. MSDG, FB and IB acquired and analyzed the stress test. BDX, SPG and RJP acquired and analyzed the MRI data. The SSA was done by GB, MAGB, CB and MDC. All authors participated in the data interpretation, reading and approval the final manuscript.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Comité ético de investigación clínica del Hospital Clínic de Barcelona) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Tables

Table 1 Demographics and echocardiographic functional measurements of the population, in the format of mean (STD).

	Athletes	Controls	p-value
Age [y]	35.4(6.1)	33.4(3.8)	0.013
BSA [m^2]	1.78(0.19)	1.86(0.20)	0.005
Weight [kg]	66.8(11.3)	73.5(15.1)	0.001
Height [m]	1.71(0.09)	1.73(0.08)	0.151
Women [%]	42(48%)	32(44%)	0.938
HR - echo [bpm]	57.2(8.4)	65.8(10.6)	< 0.001
LV EF [%]	54.6(4.4)	62.6(5.6)	< 0.001
SV [ml/m2]	47.5(9.5)	40.2(8.6)	< 0.001
CO [l/min/m2]	2.7(0.6)	2.6(0.5)	0.302
RV FAC [%]	45.2(5.2)	45.6(8.7)	0.767
TAPSE [mm]	25.9(2.9)	25.3(3.4)	0.197
VO2 peak [l/min/m^2]	1.63(0.28)	1.11(0.28)	< 0.001

(BSA: body surface area, HR: heart rate, LV EF: left ventricular ejection fraction, SV: stroke volume, CO: Cardiac output, RV FAC: right ventricular fractional area change, TAPSE: tricuspid annular plane systolic excursion, VO_2 max: Maximal oxygen uptake)

Table 2 Comparison of the MRI- based measurements between athletes and controls. All measurements were computed from the MRI-derived 3D model .

	Athletes	Controls	p-value
LV EDV [mL/m^2]	101.7(17.4)	82.9(12.1)	< 0.001
LV Mass (3D) [g/m^2]	83.7(14.0)	71.7(11.4)	< 0.001
LV LA[mm/ m^2]	53.9(4.2)	49.4(4.2)	< 0.001
LV OT [mm/ m^2]	14.6(1.0)	13.4(0.9)	< 0.001
RV EDV [mL/m^2]	108.3(22.6)	86.4(15.7)	< 0.001
RV EDA [cm^2/m^2]	18.0(2.6)	15.7(2.2)	< 0.001
RV LA [mm/m^2]	51.8(3.8)	47.2(3.9)	< 0.001
RV Basal Dimension [mm/m^2]	28.1(2.5)	25.8(2.4)	< 0.001
RV OT [mm/m^2]	16.6(1.4)	15.0(1.1)	< 0.001

(LV EDV: left ventricular end-diastolic volume, LV LA: left ventricular long axis, LV OT: left ventricular outflow tract, RV EDV: right ventricular end-diastolic volume, RV EDA: right ventricular end-diastolic area RV LA: right ventricular long axis, RV OT: right ventricular outflow tract)

Table 3 : Results of the MVR to check the relationship between shape remodeling score to different functional parameters during exercise. Only athletes are included in this analysis. The p-values were obtained by comparing the regression model involving the athletic remodeling score and the confounders with a model that uses only confounders with a Fisher F-test.

	Standardized coefficient	**R^2**	**P Value**
Resting HR	-0.18	0.08	0.03
Maximal HR	-0.17	0.19	0.08
Baseline VO_2	-0.10	0.09	0.50
Peak VO_2	0.20	0.49	<0.01
Peak oxygen pulse	0.26	0.51	< 0.001
Baseline RV GLS	-0.17	0.29	0.11
Post-exercise RV GLS	0.04	0.41	0.69
RVGLS resere	0.29	0.24	0.03
Resting LV GLS	0.02	0.31	0.84
Post-exercise LV GLS	0.11	0.30	0.23
Resting LV EDV	0.67	0.73	< 0.001
LV myocardial volume	0.50	0.72	< 0.001
LV EDV increase ratio	0.02	0.01	0.70
Resting RV EDV	0.61	0.69	< 0.001
RV EDA increase ratio	-0.10	0.05	0.24

(VO_2: oxygen uptake, RV GLS: right ventricular global longitudinal strain, LV GLS: left ventricular global longitudinal strain, LV EDV: left ventricular end-diastolic volume, RV EDV: right ventricle end-diastolic volume)

Figures

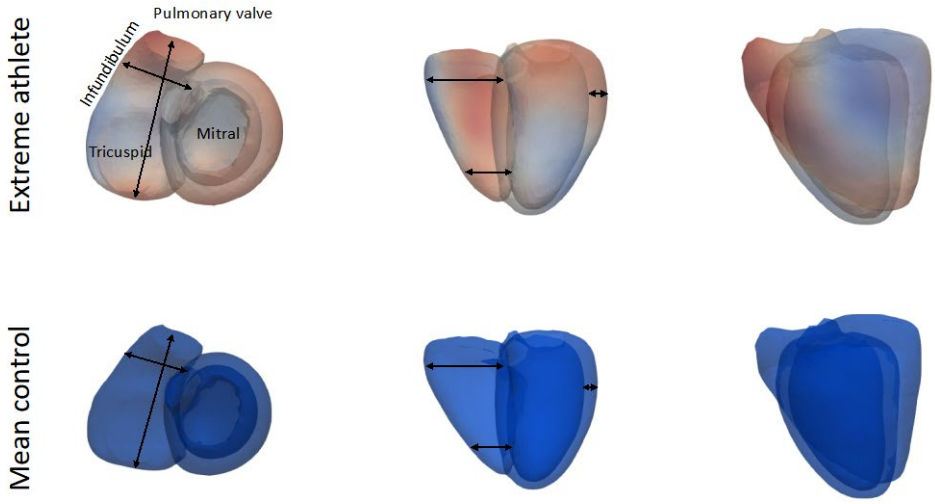

Figure 1 Most discriminant shape mode that distinguishes the RV from athletes and controls. The upper row corresponds to a representative extreme athlete (population mean + 3STD of athletic remodeling), and the lower one to the mean shape of the non-athletes. The three views correspond to: a view of the base from the atria (left), a longitudinal view of the inferior RV and LV walls (center), and a longitudinal view of the LV free wall (center). The red-blue color map indicates in red the regions that present more remodeling, and the purple lines the observed differences. Both ventricles are very different from the controls, but while the LV mostly scale, more regional shape changes occur in the RV, especially in the outflow.